d) seeding the isolated cells in a carrier material such that the isolated cells are dispersed and distributed in the carrier material forming a three-dimensional structure; and

e) culturing said dispersed and distributed cells in the three-dimensional structure.

REMARKS

Consideration of this Amendment After Final Rejection is respectfully requested. Claims 10, 11, 13-15 and 18-34 remain in the application. The independent claims have been amended to limit all of the claims to annulus disc cells.

Claim Objections

Claim 10, line 3 has been objected to because "obtain" should read –obtained--. Correct has been made in Claims 10 and 14.

Claim Rejection - 35 U.S.C. § 112,¶1

The sole remaining rejection is that the claims have been rejected under 35 U.S.C. § 112,¶1 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In making this rejection the Examiner has raised several issues that are discussed below.

As previously noted the, in early childhood the intervertebral disc consists of a peripheral annulus and a central nucleus. The intervertebral disc and particularly its nucleus undergo continuous change during development, maturation, and degeneration. The nucleus disappears in early childhood and becomes fibrocartilaginous in adolescents and adults. The annulus becomes almost avascular in adults. *See*, Taylor and Twomey, "*The development of the human intervertebral disc.*" Chap.2 in Vol.1., p. 40, The biology of the Intervertebral Disc. P.Ghosh, ed. CRC Press, Boca Raton, FL. 1988). The type of intervertebral disc cells that were cultured in the therapeutic composition and used in the methods claimed for this invention included cells from the annulus region. The specification discusses the use of annulus and nucleus cells in this

invention and while annulus cells have been used it would not matter if there were a few cells from the nucleus region of the disc. *See Specification, page 5, lines 13-14.* The Declaration of Dr. Helen Gruber is submitted herewith. Dr. Gruber, confirms that annulus cells were used in her studies and in paragraph 6, states: "In my opinion, the patent application provides sufficient guidance for one skilled in the art to provide the claimed composition using disc cells from the annulus."

In the amendment filed February 26, 2001 the Applicants discussed several references intended to show the growth of cells in humans. These references included publications by Walmsley; Taylor and Twomey; Butler; and Errington. Copies of these publications were inadvertently omitted when filing the amendment. They are now enclosed.

The Examiner next questions whether the cells in the therapeutic composition are de-differentiated, proliferating cells, or whether the cells are differentiated and secreting an extra cellular matrix that is representative of the matrix observed in a normal intervertebral disc *in vivo*. The annulus cells are proliferating cells. The state of differentiation would be either de-differentiated (flattened cells grown in monolayer on traditional plastic cultureware) or differentiated (rounded cells) grown in three-dimensional microenvironments such as alginate, agarose, or collagen sponges. Dr. Gruber conducted studies of the growth of annulus cells of the therapeutic composition. Dr. Gruber showed that the annulus cells of the sand rat were proliferating cells. *Declaration of Dr. Gruber, Paragraph 8, Exhibit B, Figures A and B.*

In addition, Dr. Gruber's studies show that the cultured annulus disc cells in the therapeutic composition are secreting extracellular matrix components including type I collagen, type II collagen, chondroitin sulfate and keratin sulfate. The results are shown in Figures C-F of Exhibit B, wherein secretion of extracellular matrix components can be seen. *Declaration of Dr. Gruber, Paragraph 9, Exhibit B, Figures C-F.*

According to the Examiner, "Given the heterogeneity of disc architecture and composition, and the lack of teaching in the specification as to which cell type is required for implanting such that the appropriate matrix is elaborated and is therapeutically effective in treating disc diseases, it would require undue experimentation to make and use the invention as

claimed." Having shown and claimed the use of annulus cells in the therapeutic compositions of this invention, it is Dr. Gruber's opinion that the reasons for the so-called lack of teaching in the specification has been clarified and thus, it would not require undue experimentation to make and use the invention as claimed. *Declaration of Dr. Gruber, Paragraph 10, Exhibit B.*

In summary, while Applicants do not argue that no experimentation to practice the invention is required, each of the issues raised by the examiner has been clarified which illustrates that there is sufficient guidance in the specification such that *undue experimentation for one skilled in the art* is not required. It is therefore respectfully submitted that the methods of treating disc disease meet the requirements of 35 U.S.C. §112, ¶1.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on July 23, 2001.

Tamara. Stevens

Version with Marking to Show Changes Made:

10. (Twice amended). A therapeutic composition for use in treating human disc diseases comprising an implantation carrier in the form of a hydrogel in admixture with *in vitro* propagated human intervertebral annulus disc cells, said disc cells being obtained from a monolayer human intervertebral annulus disc cell culture prepared by a method comprising the steps of:

a) providing a minced human intervertebral annulus disc tissue explant comprising human intervertebral disc cells; and

b) culturing said minced explant under conditions to propagate and form a monolayer of human intervertebral disc cells, wherein the human intervertebral disc cells of said monolayer can be isolated and further propagated upon passaging.

14. (Twice Amended). A therapeutic composition for use in treating human disc diseases comprising an implantation carrier in admixture with *in vitro* propagated human intervertebral annulus disc cells, said disc cells being obtained from a three-dimensional human intervertebral annulus disc cell culture prepared by a method comprising the steps of:

a) providing a minced human intervertebral annulus disc tissue explant comprising human intervertebral disc cells;

b) culturing said minced explant under conditions to propagate and form a monolayer of human intervertebral disc cells, wherein the human intervertebral disc cells of said monolayer can be isolated and further propagated upon passaging;

c) isolating the human intervertebral disc cells from said monolayer;

d) seeding the isolated cells in a hydrogel carrier material such that the isolated cells are dispersed and distributed in the carrier material forming a three-dimensional structure; and

e) culturing said dispersed and distributed cells in the three-dimensional structure.

19. (Once amended). A method for treating an intervertebral disc disease in a human patient, comprising implanting *in vitro* propagated human intervertebral annulus disc cells into a target disc area needing treatment in said human patient.

25. (Once amended). The method of Claim 20, wherein said process further include *in vitro* propagated human intervertebral annulus disc cells are provided by a process including the steps of:

a) providing said human intervertebral annulus disc tissue to obtain a minced explant comprising human intervertebral disc cells;

b) culturing said minced explant under conditions to propagate and form a monolayer of human intervertebral disc cells, wherein the human intervertebral disc cells of said monolayer can be isolated and further propagated upon passaging;

c) isolating said human intervertebral disc cells from said monolayer;

d) seeding the isolated cells in a carrier material such that the isolated cells are dispersed and distributed in the carrier material forming a three-dimensional structure; and

e) culturing said dispersed and distributed cells in the three-dimensional structure.